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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/612,121	07/02/2003	Jamie L. Brewer	260385.20005	6561

7590 10/16/2008

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EXAMINER	
JUEDES, AMY E	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
10/16/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/612,121	BREWER ET AL.	
	Examiner	Art Unit	
	AMY E. JUEDES	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1-14,17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-16 and 19-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 8/6/08 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/6/08 has been entered.

Claim 20 has been added.
Claims 1-20 are pending.

Claims 1-14 and 17-18 stand withdrawn from further consideration pursuant to 37 CFR 1.14209 as being drawn to a nonelected invention.

Claims 15-16 and 19-20 are under examination.

2. **Claims 15 and 19-20 are objected to because of the following informalities: The claims are objected to for referring to the sequences in Table 2.** Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." *Ex parte Fressola*, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993). **In the instant case, it appears that the sequences of Table 2 are the same as SEQ ID NOs: 33-55. Thus, the reference to table 2 is not necessary to define the invention. Rather, the claims could recite a kit comprising nucleic acid sequences consisting of SEQ ID NO: 33—55, for example. Appropriate correction is required.**

3. Upon reconsideration, the rejection of the claims under 35 U.S.C. 112 first paragraph for lack of written description is withdrawn. However, Applicant's arguments relevant to the new grounds of rejection will be addressed below.

4. The following are new grounds of rejection.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 15-16 and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, there is insufficient written description to demonstrate that applicant was in possession of the claimed genus of "variations" of SEQ ID NOs: 33-55 that differ by "no more than 8 nucleotides" or "no more than 2 nucleotides".

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

The instant claims encompass a genus of nucleic acid variants that differ by up to 8 nucleotides from the sequences of SEQ ID NOs: 33-55. The sequences of SEQ ID NOs: 33-55 comprise as few as 18 nucleotides. Thus, the instant claims encompass structurally different "variations" that differ by up to approximately 40% from the sequences of SEQ ID NO: 33-55. Furthermore, even when the claims are limited to variations of no more than 2 nucleotides, this still encompasses structurally different sequences varying up to approximately 10% from the sequences of SEQ ID NOs: 33-55. The instant claims are drawn to a kit for assessing the expression of T cell receptor variable subunit β, and thus the claimed sequences must implicitly function to assess said T cell receptor expression. The specification does not disclose a correlation between the

structure of the claimed sequences, and their ability to function to asses T cell receptor variable subunit β. Additionally, the state of the art is such that the ability of nucleic acid sequences to function as primers for assessing the expression of TCR variable expression is highly complex (see Genevee et al., 1992, page 1264 in particular, of record). Thus, there is no art recognized correlation between the structure of the claimed nucleic acid molecules and the ability to determine TCR expression. Furthermore, the instant specification does not disclose a single species of sequence that is a "variation" of SEQ ID NOs: 33-55. Thus, one of skill in the art would conclude that the specification fails to provide adequate written description to demonstrate that Applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F. 3d 1559, 43, USPQ2d 1398.

Applicant's arguments filed 8/6/08 have been fully considered, but they are not persuasive.

Applicant argues that the specification discloses in paragraph 10 that the nucleotide sequences of SEQ ID NOs: 1 through 55 may differ by up to eight nucleotides, but more often by one or two nucleotides, and thus provides adequate written description for the claimed invention.

As noted above, the instant claims are drawn to a genus of "variant" nucleic acid sequences. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see MPEP 2163). While the specification generically discloses the genus of variants recited in the claims, no representative species are disclosed, nor is there a disclosure of a correlation between the structure of the claimed variants, and their ability to function to assess TCR variable expression.

7. Claim 20 is rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not

reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A kit for assessing the expression of T cell receptor variable subunit β, said kit comprising SEQ ID NOs: 33-55 and "variations thereof that consist of no more than eight additional nucleotides in total appended to either end of the SEQ NOs: 33-55".

It is noted that applicant has not cited any support for the new limitation in the specification. A review of the specification fails to reveal support for the new limitations.

At page 8, the specification discloses nucleotide sequences that differ by up to 8 nucleotides from SEQ ID NOs: 33-55. However, the specification does not disclose variations of no more than 8 nucleotides "appended to either end of SEQ ID NO: 33-55", as now claimed.

8. Claims 15-16 and 19-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A kit for assessing the expression of T cell receptor variable subunit β, said kit comprising nucleic acid sequences consisting of SEQ ID NOs: 33-55,

does not reasonably provide enablement for:

A kit for assessing the expression of T cell receptor variable subunit β, said kit comprising nucleotide sequences that are variations of SEQ ID NOs: 33-55 that differ by no more than eight nucleotides, nucleotide sequences that are variations of SEQ ID NOs: 33-55 that differ by no more than two nucleotides, and nucleotide sequences that are variations of SEQ ID NOs: 33-55 that consist of not more than eight additional nucleotides in total appended to either end of SEQ ID NOs: 33-55.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art,

the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. With these teachings in mind, an enabling disclosure, commensurate in scope with the breadth of the claimed invention, is required.

The instant claims are drawn to kit for assessing the expression of T cell receptor variable subunit β, said kit comprising nucleic acid molecules that consist of SEQ ID NOs: 33-55 and variations thereof that differ by no more than 8 nucleotides, or no more than 2 nucleotides. The claims further recite that the kits might comprise variations of SEQ ID NOs: 33-55 that consist of no more than 8 additional nucleotides appended to either end of SEQ ID NOs: 33-55. SEQ ID NOs: 33-55 represent oligonucleotide primer sequences that the specification discloses can be used to determine TCR Vβ expression by methodologies such as PCR. The claims encompass a range of structurally different primer variants comprising as many as 8 insertions, deletions or mutation to the primer sequences of SEQ ID NOs: 33-55. Furthermore, the claims encompass addition of up to 8 nucleotides to either end of the primer sequences, with no requirement that the added nucleotides correspond to any Vβ sequence. PCR requires a myriad of complex interactions between template and primers to accomplish target amplification (see Kwok et al., 1994). Even single base

mismatches can significantly lower the melting temperature of primer to template, and reduce the amplification yield (see Kwok et al., 1994, page S39 and S41). Furthermore, mismatches at the 3' terminus of a primer are more detrimental to PCR than internal mismatches (see Kwok et al., 1994, page S39 in particular). Thus, the functional ability of the "variant" sequences, including variants with nucleotides appended to the end of the sequences (particularly the 3' end) would be extremely unpredictable. Furthermore, primer design to assess TCR variable gene expression is extremely complex due to the nature of the TCR which comprises many variable families that display various levels of nucleotide similarity. For example, a major requirement for the design of Vβ specific primers is template specificity, and a given primer should strongly anneal to the intended target sequences, including all members of the subfamily, and not base pair to other regions within the template or to similarly located nucleotide regions of the TCR V gene segments belonging to a different subfamily. In fact, difficulties frequently arise for members belonging to a subfamily including multiple disparate genes sequences or when studying a subfamily which includes gene segments that share a high degree of nucleotide similarity with V gene segments from another subfamily (see Genevee et al., 1992, page 1264 in particular, of record). Thus, designing primers that can distinguish the various variable β subunit family members, as is encompassed by the instant claims, is extremely complex and unpredictable.

Thus, given the unpredictability of the art the instant specification must provide a sufficient disclosure to enable one of skill in the art to use the variant nucleic acid sequences to assess the expression of T cell receptor variable subunit β, as claimed. However, the only Vβ specific nucleotide sequences disclosed by the instant specification are SEQ ID NOs: 33-55. The specification does not disclose any variant sequences, nor does it provide any guidance as to which nucleotides can be varied, while still maintaining their ability to discriminate TCR Vβ gene expression. Thus, given the unpredictability of the art and the lack of guidance provided by the instant specification, it would require undue experimentation to make and use the claimed "variant" nucleic acid molecules to assess TCR Vβ expression as broadly claimed.

9. No claim is allowed. Claims 15-16 and 19-20 are free of the

prior art.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, Ph.D. whose telephone number is 571-272-4471. The examiner can normally be reached on 6am - 2pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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